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Paying for “End-of-Life” Drugs in Australia, Germany, and the United Kingdom: Balancing Policy, Pragmatism, and Societal Values

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ABSTRACT: Balancing sustainability with equitable access to new technologies is a challenge for all health systems. For instance, potentially life-extending but expensive medicines, particularly in oncology, may offer only modest benefit near the end of life. The costs of these drugs are placing pressure on public and private payers, individual patients, and their families. The United Kingdom and Australia have established programs that require evidence of comparative clinical and cost-effectiveness to inform decisions. This brief analyzes British, Australian, and German policies on coverage of such medicines. For Europe and Australia, the challenge is to manage the continuing pressure to pay for expensive medicines through tax- or social security-funded systems, without undermining core principles of equity and efficiency. For the United States, the challenge is to ensure fiscal sustainability of Medicare, Medicaid, and the private insurance market without restricting choice, especially as health reform extends access to more Americans.

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INTRODUCTION

Balancing sustainability and cost containment with equitable and timely access to effective new technologies is a challenge around the world. Expensive medicines that potentially extend life, particularly those used in oncology, are placing cost pressures on public and private payers, as well individual patients and their families.¹ To address these tensions, the United Kingdom, Australia, and Germany have well-established programs that require evidence of comparative clinical and, for Australia and the U.K., cost-effectiveness to inform resource allocation decisions. This issue brief compares U.K., Australian, and German policies on coverage of these medicines, particularly those that are not curative and offer modest increments in

median survival rates. Based on analyses of published policies, legislation, and grey literature from each of the three countries, as well as individual case studies and aggregate data on coverage decisions and spending, we discuss the methodological, evidential, and ethical challenges of using comparative effectiveness research to inform coverage decisions for end-of-life medicines. We identify insights for the United States; in particular, for the Patient-Centered Outcomes Research Institute that is charged with developing appropriate evidence to guide decision-makers across the various U.S. health care sectors.

Despite the significant structural and cultural differences between the U.S. system and the U.K., German, and Australian systems, all four countries face similar challenges with respect to evidence-informed pharmaceutical policy. For Europe and Australia, the aim is to manage the burgeoning pressures to pay for expensive cancer drugs for patients with incurable diseases through a resource-constrained system funded through taxes or social security, without undermining the core principles of equity and efficiency. For the United States, it is about ensuring the fiscal sustainability of Medicare, Medicaid, and the private insurance market—especially as the implementation of the Affordable Care Act broadens access to more Americans—without restricting choice or causing a backlash from those who are well-insured or the health care industry. With prices escalating across developed markets and affordability an issue for U.S. insurers and national health system administrators,^{2,3} there is an ongoing battle to reconcile sustainability with access, equity, and industry policy.

THE U.K.'S NATIONAL HEALTH SERVICE: EXCEPTIONAL POLICIES AND PRICE NEGOTIATIONS

In the United Kingdom, a recent public debate has prompted the National Institute for Health and Clinical Excellence (NICE) to introduce a specific policy to guide decision-making around expensive, mainly oncologic medicines, by creating a mechanism that effectively allows its committees to approve seemingly cost-ineffective drugs where they are thought to extend life in terminally ill

patients. This is known as end-of-life (EOL) guidance. In addition, the new U.K. coalition government has announced the establishment of a Cancer Drugs Fund to support access to any medicine an oncologist feels is clinically appropriate, thereby raising significant concerns around both costs and feasibility. The Fund would operate until the new value-based pricing policy is put in place in 2014, which is intended to ensure all drugs launched in the U.K. market are priced in an appropriately cost-effective way and can be made available to all who need them. This section describes the three initiatives (EOL, Cancer Drugs Fund, and value-based pricing) and discusses their possible implications on access, equity, and overall costs. This is followed by a discussion of risk-sharing schemes (known as patient access schemes), a policy that allows NICE's committees a third option in addition to a positive or negative adoption decision.

NICE's End-of-Life Guidance: Introducing Managed Flexibility

NICE was established in 1999 to reduce inappropriate variation, known as the “postcode lottery,” in access to treatments; accelerate the uptake of innovative treatments (mostly drugs) across the country, given the relatively conservative prescribing habits of British physicians; set nationwide, evidence-based clinical guidelines for professionals; and ensure resources are invested in the National Health Service (NHS) in the most cost-effective way.⁴

In August 2008, NICE's technology appraisal committee, responsible for making recommendations to the NHS on the value of pharmaceuticals and other medical technologies, published draft guidance rejecting the use of Sutent for metastatic renal cancer because it was not cost-effective. In addition to Pfizer's Sutent, the committee provisionally ruled against bevacizumab, sorafenib, and temsirolimus for the same indication. NICE estimated it would cost from £70,000 to £170,000 (US\$113,000 to \$275,000) per patient per year to offer these drugs for an average life extension of no more than a few weeks. In March 2009, the guidance was partly reversed and NICE recommended “sunitinib as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy”⁵

A great deal occurred in the interim. Following a very public debate in the press, repeated consultations on the individual drug submissions that included additional evidence from the manufacturers, a NICE Citizens’ Council recommending that disease severity be accounted for in coverage decisions,⁶ and two NICE Board meetings, NICE issued guidance to its own committees to change the way it evaluates drugs that extend life for terminally ill patients. This end-of-life (EOL) guidance was the conclusion of an almost 12-month debate to how the NHS could improve access to expensive cancer drugs.^{7,8} NICE’s EOL guidance came as a response to a review commissioned by the U.K. The review was tasked to find ways for improving access to medicines through the tax-funded NHS without burdening patients with out-of-pocket contributions.⁹ Responding to the review, NICE issued guidance to its committees to be more generous when evaluating clinical and cost-effectiveness when assessing “treatments licensed for terminal illnesses affecting small numbers of patients, which, although offering demonstrable survival benefits over current NHS practice, need a significantly higher share of NHS resources to pay for them than is normally the case for effective new treatments.”¹⁰ The criteria set forth in the EOL guidance (Exhibit 1) resulted in about a dozen drugs being reviewed from January 2009 to late 2010, with half gaining “exceptional” approval, despite the fact that their incremental cost-effectiveness ratio was above NICE’s £20,000 to £30,000 (US\$32,000 to \$49,000) per quality-adjusted life year.¹¹

The U.K.’s Cancer Drugs Fund: Coming Full Circle

The NICE EOL policy was not intended to ensure that all new treatments—particularly new cancer drugs—could be covered by the NHS. Instead, the objective was to be able to show flexibility, and to take social value judgments into consideration, while still quantifying the opportunity cost of adoption decisions and sustaining the pressure on pharmaceutical manufacturers to produce credible value propositions for their products. As a result, NICE still rejected drugs such as sorafenib for advanced liver cancer and bevacizumab for first-line renal cancer. The pressure from patient groups and the pharmaceutical industry continued, as did the press coverage, and cancer treatment became an electoral campaign commitment for the opposition. In its manifesto, the Conservative Party promised to pay for all cancer drugs. The coalition plan for government, published in July 2010, states: “We will create a Cancer Drugs Fund to enable patients to access the cancer drugs their doctors think will help them.”¹²

The announcement of the Cancer Drugs Fund triggered both positive and negative reactions. While some patient groups and the drug industry welcomed the move, *The Lancet* speculated, “Presumably emergency funds for dementia and multiple sclerosis drugs will be announced in due course—anything else would be intellectually indefensible.”¹³ Despite government’s reassurances that the Fund did not undermine NICE and was part of a broader policy for improving access to drugs, some felt it did precisely that.¹⁴

Exhibit 1. NICE Criteria for Applying End-of-Life Guidance to Committee Decisions on Drugs

NICE’s EOL advice should be applied when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared with current NHS treatment, and;
- The patient population for which the treatment is licensed or otherwise indicated is small.

When applying the EOL guidance, NICE’s committees ought to:

- Be convinced of the robustness of the data;
 - Quantify (and state) how much more the new drug has to be valued (compared with alternatives) to be deemed cost-effective by NICE’s conventional standards; and
 - Recommend data collection in order to evaluate the true survival benefit conferred by the drug.
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Less than a year following its launch, two major practical problems became apparent. One was estimating the magnitude of funding necessary to cover all cancer drugs rejected by NICE, the other was offering all patients eligible to benefit from it equal access across the country. On the former, government relied on, among others, estimates from the Rarer Cancers Forum,¹⁵ suggesting that £200 million (US\$324 million) per year would be enough to cover all cancer drugs that NICE had not approved on the grounds of inadequate cost-effectiveness. Starting with £50 million (US\$81 million) for part of 2010, the Fund has grown to £200 million per year from 2011 onwards. However, £200 million is unlikely to be enough. Bevacizumab for bowel cancer (rejected by NICE in December 2010) would take up almost 70 percent of the Fund's annual budget, or £135 million (US\$219 million) per year for England alone.¹⁶ The second problem is administering the Fund in an equitable fashion. Lack of centralized guidance is, once again, resulting in practice variations and is triggering complaints from professionals and patients.

In addition to the practical problems of getting the size and disbursement right across the country, the ethical basis for singling out cancer as distinct from the many other severe end-of-life conditions is unclear. The government's impact assessment to accompany the new policy noted that "no evidence has been found for prioritizing cancer above other severe conditions, or for prioritizing drug treatments above any other interventions for cancer."¹⁷

PATIENT ACCESS SCHEMES AND VALUE-BASED PRICING: CAN THEY IMPROVE PATIENTS' ACCESS TO NEW DRUGS?

While NICE cannot negotiate prices, it has been increasingly using price deals with manufacturers to improve patients' access to technologies, often coupled with the application of EOL guidance.¹⁸ Such deals, formalized as patient access schemes, effectively reduce the cost of the drug to the NHS without affecting the list price of new drugs launched in the U.K. market.¹⁹ The latter is important as, despite the U.K. market's relatively small size (3% of the global pharmaceutical market), NHS prices are

internationally referenced by a quarter of the global market.²⁰ Patient access schemes began as risk-sharing mechanisms, with the first being for Velcade (bortezomib), a drug for multiple myeloma.²¹ In 2007, the manufacturer and NICE agreed to an arrangement that would ensure access for NHS patients and at the same time satisfy NICE's requirements for evidence of comparative clinical and cost-effectiveness prior to diffusion. The company committed to reimbursing NHS providers if the drug did not work (based on a reliable test of response to treatment) and the NHS promised to pay for the drug for all those patients that did respond. The response threshold was negotiated and the scheme launched. Since then, over 20 technologies, mostly expensive pharmaceuticals, have been made available to the NHS through similar programs. Increasingly, these are now being used as a means of negotiating price reductions through capping the overall number of treatment cycles or treatment costs to those of the next best alternative, effectively leading to a reduction in prices and more favorable incremental cost-effectiveness ratios. Nevertheless, despite the advent of patient access schemes and the EOL policy, NICE is still unable to recommend access for around 30 percent of the cancer drugs it reviews on grounds of inadequate clinical or cost-effectiveness.²²

To improve access to expensive new medicines, the new government has announced radical reforms in the way pharmaceuticals are priced and launched in the U.K. Starting in 2014, the government will negotiate prices of all new drugs before they can enter the U.K. market. In addition to NICE's analysis of comparative clinical and cost-effectiveness, the negotiation will consider broader societal benefits, disease severity, and the degree of innovation represented by the new therapy.^{23,24} The government is "determined to create a system that gives patients access to the most effective medicines . . . too often, the NHS has been in the position of either having to pay high prices that are not always justified by the benefits of a new medicine, or having to restrict access . . . There must be a much closer link between the price the NHS pays and the value that a medicine delivers."²⁵

Reorganization of the NHS: NICE’s Future Role

The United Kingdom is committed to an NHS that is free at the point of delivery, based on need and not the ability to pay. Although the NHS is currently undergoing one of its most radical reorganizations since it was established in 1948, the role of NICE in ensuring quality, efficiency, and equitable access has been reinforced by the current government. Beginning in 2012, NICE will assume responsibility for setting standards in social care (e.g., home care for the elderly), and it is likely to have a broader role in informing price-setting for pharmaceuticals from 2014. In addition, primary legislation will reestablish the organization as accountable to Parliament rather than to the Department of Health from 2012. Perhaps most important, NICE is now responsible for setting quality standards that will drive purchasing and delivery of services, as well as pay-for-performance in primary and secondary care and provider regulation.²⁶

END-OF-LIFE DRUGS AND DRUGS FOR RARE DISEASES IN AUSTRALIA

Australians have benefited from universal access to subsidized prescription medicines since 1948. The Australian Pharmaceutical Benefits Scheme (PBS) is a federal government program that operates under the umbrella of the National Medicines Policy, which aims to provide “timely access to the medicines that Australians need, at a cost individuals and the community can afford.”²⁷ Subsidized medicines are listed on a national formulary, with inclusion processes intended to support affordable, equitable access to prescription medicines and ensure value for Australian taxpayers, and not necessarily as a mechanism for cost containment.

The inclusion of a drug on the national formulary is dependent on a positive recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC), which considers not only the comparative effectiveness of proposed drugs but also their comparative cost-effectiveness. The PBAC is a statutory, independent, expert committee established under the National Health Act of 1953 to make recommendations to the Minister for Health and Ageing on which medicines should be included on

the schedule of pharmaceutical benefits and any conditions that should apply. A 1987 amendment to the Act required PBAC to take into account the effectiveness and cost of a medicine compared with other drug or nondrug therapies when considering listing a new medicine on the formulary.²⁸ As a result, a medicine that is more costly than other available treatments is generally only recommended for subsidy if it represents a clinically significant improvement in effectiveness or reduction in toxicity.²⁹

While the recommendations of the PBAC are advisory only, and the final listing decision remains with the Minister for Health and Ageing,³⁰ the Minister may decline a listing recommendation made by the PBAC, but cannot add a medicine to the PBS formulary in the absence of a positive recommendation from the committee. Here we describe some of the flexibilities within the PBS listing decision-making processes and look at other programs established within Australia to address exceptional circumstances such as end-of-life treatments and expensive drugs for rare, life-threatening diseases.

PBAC Decision-Making

While comparative cost-effectiveness is an essential prerequisite for listing, it is not the sole criterion nor does PBAC apply a fixed cost-effectiveness threshold. As such, it is able to be both more and less flexible than the U.K.’s NICE. The PBAC applies a similar decision-making paradigm to all medicines irrespective of the therapeutic area, so no particular significance is attached to an oncology or other “end-of-life” medicine. Rather, in considering each submission, the committee weighs a range of relevant factors in addition to incremental cost-effectiveness. These factors are not weighted equally but by their relative importance in different situations, making it impossible to quantify the importance of any particular factor. The factors are:

- clinical need, particularly for conditions for which there are no, or few, treatment options;
- the extent to which a proposed treatment represents a clinically meaningful advance in therapy;
- the degree of uncertainty in the estimate of incremental cost-effectiveness;

- the potential total cost to the PBS or government health budgets;
- the scope for use of the drug beyond any restriction for subsidy, and the extent to which a restriction can be constructed that satisfactorily distinguishes use that is acceptably cost-effective from use that is not cost-effective;
- the potential for adverse outcomes arising from availability with subsidy (e.g., PBAC may restrict subsidized use of certain antibiotics to limit the development of resistant organisms);
- the affordability of the medicine to the patient in the absence of a subsidy; and
- the “rule of rescue”—reserved for drugs for serious or fatal diseases for which no other treatments are available.

The Rule of Rescue

It is this last factor—the so-called “rule of rescue”—through which the PBAC may apply some additional flexibility when considering an end-of-life drug. However, it is applied rarely; it is reserved strictly for medicines for life-threatening conditions for which there is no other effective treatment available in Australia, either subsidized or unsubsidized (see Exhibit 2). The rule of rescue supplements, rather than supplants, the consideration of comparative cost-effectiveness. A decision on whether the rule is relevant is taken only if PBAC is inclined to reject a submission on comparative cost-effectiveness grounds. In this situation, if PBAC concludes that the rule is relevant, it will then consider whether it is sufficiently influential to reverse the decision not to recommend listing.

Restricted Indications

As the PBAC continues to grapple with expensive end-of-life drugs, listing recommendations may be accompanied by closely specified restrictions and, at times, “stepped-therapy”³¹ requirements or treatment algorithms. These are imposed because drugs either lack robust evidence of a clinically important additional benefit over existing therapies or because the incremental costs of obtaining those benefits mean that the drugs are cost-effective in only a defined group of patients. The PBAC, in attempting to facilitate access and ensure taxpayer value, may at times recommend that subsidized access be limited to so-called “last-line” therapy (i.e., treatments that are reserved for circumstances where all alternative therapies are unsuitable or have not proven successful for an individual patient); in other cases, it may recommend that access be highly targeted, or, in a small number of cases, that subsidized therapy be continued only for patients who demonstrate a predefined response to the treatment.

Risk-Sharing Arrangements

The PBS uses a variety of risk-sharing arrangements (RSAs), which are similar to the U.K.’s patient access schemes.³² One example of an RSA is a rebate paid to government by the manufacturer for PBS’s expenditures on a particular drug exceeding an agreed-upon annual cap. In some cases a pooled annual sales cap may be established for a group of drugs used to treat a particular condition, with rebates proportional to market share. Price-volume agreements (the very first RSAs) provide rebates or price reductions based on the price of an alternative, cheaper medicine when use exceeds the estimate of the population in whom the medicine is considered to

Exhibit 2. PBAC Guidance on the Application of the “Rule of Rescue”

Four factors, which apply in exceptional circumstances, are particularly influential in favor of listing. When all four factors apply concurrently, this is called the “rule of rescue.”

- No pharmacological or nonpharmacological alternative exists in Australia to treat patients with the medical condition;
 - The medical condition is severe, progressive, and expected to lead to premature death;
 - The medical condition applies to only a very small number of patients; and
 - The proposed drug provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition.
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be cost-effective and when it is difficult to restrict use to a particular subpopulation.

Although dispensed prices for PBS medicines and other formulary information are in the public domain, RSAs may also reduce the actual price paid by the PBS program without affecting the published dispensed price of a drug. A number of medicines listed on the PBS formulary carry the notation that “special pricing arrangements apply,” indicating that the list price is at variance with the true transaction cost. This improves value for money but reduces transparency in pricing.

Herceptin: A Special Case

The case of Herceptin (trastuzumab) reflects a singularly awkward episode in the PBAC’s history. In Australia, regulatory approval of Herceptin in 2000 was immediately followed by extensive campaigning by patient groups in favor of subsidized access through listing on the PBS—for what was then one of the most expensive medicines ever considered for listing. In assessing the sponsor’s application in 2001, the PBAC did not consider the drug to be sufficiently cost-effective for the treatment of metastatic breast cancer and rejected the application. Throughout 2001, interest groups heavily lobbied the prime minister, minister for health, and other key politicians, as well as PBAC, to support PBS listing of the drug. This led to pre-election commitments from both major political parties to subsidize Herceptin.

However, as it was unable to list the medicine on the PBS in the absence of a positive recommendation from the PBAC, the government created a separate, taxpayer-funded Herceptin program outside the PBS,³³ which continues today. Despite being PBS-listed for early-stage breast cancer in 2006, subsidized access to Herceptin in advanced metastatic disease remains limited to this special program—an arrangement that has not, to date, been repeated. Indeed, the ongoing viability and credibility of the PBAC and PBS processes might arguably be called into question were it to occur again, at least in the absence of a formal public consultation and debate about social values and expenditure priorities.

The Life Saving Drugs Program

Although this brief is focused on end-of-life medicines, it is also relevant to mention other mechanisms that exist to manage access to extremely high-cost medicines in Australia. The Life Saving Drugs Program (LSDP) is a small, fixed appropriation funded by the Australian government established outside the PBS that provides free access for eligible patients to certain expensive and life-saving drugs for rare, serious, and usually life-threatening medical conditions. Drugs included in the LSDP must be shown to be effective in extending the lifespan of patients suffering from life-threatening diseases for which there are no other suitable, cost-effective therapies available. At the present time, the LSDP funds treatment for eight drugs and around 180 patients. Seven of the drugs are for the treatment of five lysosomal storage disorders, which are rare inherited enzyme deficiencies; the remaining therapy is for the treatment of the rare disorder, paroxysmal nocturnal hemoglobinuria.

The criteria for consideration of the addition of a drug to the LSDP do not place any restrictions on the range of conditions to be treated or the types of pharmaceutical therapies (Exhibit 3). The government requires applications be submitted initially to the PBAC. The PBAC must consider the evidence presented by the medicine’s sponsor, conclude that the medicine is not cost-effective (and therefore not suitable for listing on the PBS), and then find that it meets the LSDP program criteria. Positive findings are then considered for funding by the government on a case-by-case basis.

Political Pragmatism or Compassionate Exceptionalism?

Unlike the United Kingdom, Australia has not had an extensive public or media debate on expensive lifesaving drugs or end-of-life therapies. Indeed, to date there has been no formal debate on social value judgments and their role in PBAC decision-making. From time to time, awareness of PBAC’s consideration of a particular therapy will generate interest. Previous decisions not to recommend drugs such as Alimta (pemetrexed) for

Exhibit 3. Criteria for the Inclusion of a Medicine on the Life Saving Drugs Program

1. A rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality.
2. The disease is associated with significant shortening of expected lifespan and there is evidence to expect this will be extended by use of the drug.
3. A patient with the disease can be identified with reasonable diagnostic precision.
4. The patient should not be suffering from other medical conditions that might compromise treatment effectiveness.
5. The drug must be accepted as clinically effective, but rejected for Pharmaceutical Benefits Scheme (PBS) listing because it fails to meet the required cost-effectiveness criteria.
6. No alternative is available that can be used as a lifesaving treatment.
7. No alternative therapeutic modality (e.g., surgery, radiotherapy) is recognized as a suitable and cost-effective treatment for the condition.
8. The cost of the drug is an unreasonable financial burden on the patient.
9. The patient must be an Australian resident who qualifies for Medicare.
10. Where required, the patient must also satisfy any other specific criteria that may relate to a particular disease.

Source: Authors' analysis.

mesothelioma and Soliris (ecaluzimab) for paroxysmal nocturnal hemoglobinuria attracted both media and public interest, mainly focusing on the plight of individual sufferers and their families. But, rarely, if ever, is the price of a drug questioned, or its effectiveness, which may be exaggerated in media reports, and until very recently there has been almost no discussion of the opportunity costs of expensive therapies. Programs like the LSDP are arguably challenging to reconcile with the equity objective of the National Medicines Policy. As the LSDP continues to expand, that debate becomes further overdue.

In February 2011, the federal government announced that to return the budget to surplus as quickly as possible, no new drugs would be added to the PBS until 2013, irrespective of the recommendations of the PBAC. Moreover, rather than limiting its consideration to only those drugs with an expected net cost of more than AUD10 million per year, every drug recommended for listing by the PBAC would henceforth be subject to Cabinet scrutiny.³⁴ Not surprisingly, this was met with significant criticism from the pharmaceutical industry, providers, and patients.

In a special meeting with the Consumers Health Forum on April 29, 2011, the then Minister for Health and Ageing stated that “government recognizes and values the role of PBAC in recommending new PBS listings

to government” but, perhaps for the first time, stressed issues of opportunity cost and competing priorities in noting that it is “government’s responsibility to decide whether to list a new drug, taking into account other priorities across the health portfolio and fiscal circumstances across government . . . [B]udgets must add up and choices must be made . . . I truly struggle to understand how people fail to recognize that these difficult choices have to be made . . . just because a drug is proven to be clinically and cost-effective, doesn’t mean it’s the most urgent or pressing way to spend finite taxpayer money.”³⁵

Despite this very clear articulation of issues of opportunity cost, objections to the decision to defer new listings persisted. On September 30, 2011, the government announced that as a result of budgetary savings generated by price reductions on certain medicines, it was able to reconsider the earlier decision and would list 48 new medicines on the PBS from December 1, 2011, and also committed to not defer listing of any drugs costing less than AUD10 million a year over the coming year.³⁶

POLICIES FOR ENHANCING ACCESS TO MEDICINES IN THE UNITED KINGDOM AND AUSTRALIA: PERCEPTIONS AND IMPACT

There are various policies, currently in place or under consultation, for enhancing access to pharmaceuticals,

particularly expensive oncologic and other specialized drugs, in the United Kingdom and Australia, in addition to well-established policy interventions at the institutional level (i.e., NICE in the U.K. and PBAC/PBS in Australia). Most of these policies tend to deal with the exceptions rather than the bulk of new drugs entering these countries’ markets, which are handled by NICE and PBAC through conventional processes. In addition, most of these policies (e.g., Cancer Drugs Fund, EOL guidance) are relatively new, covering only a handful of drugs, and their impact on costs and access for eligible patients have not been systematically evaluated.

GERMANY: AN END TO UNCONTROLLED PRICES

The Legal Framework in Germany: The Situation So Far

The German social code asserts that anyone who needs a treatment is entitled to receive it. This has been made particularly clear by a high court decision in 2005³⁷ involving an appeal by a patient suffering from Duchenne muscular dystrophy who was denied an unconventional bioresonance treatment by his statutory health insurance (SHI) fund. The court decreed that treatment in the case of a life-threatening disease is an essential part of health care and that SHI funds must pay for it. This judgment implied that any treatment a patient requested would have to be made available, provided there is at least a remote chance of cure or discernible improvement in the course of the disease. However, the court qualified its ruling: “A suggestion that a clinical effect might be attained for an individual can be based on the applicant’s health status compared to other patients with the same disease who have not yet received the treatment in question, and compared to other patients with the same disease who have received the treatment in question.” This makes it clear that the court would expect some evidence to substantiate the potential benefit of the treatment.

In Germany, cancer drugs—like all other medicines—have until now been reimbursed at the prices proposed by their manufacturers. Drugs are covered from market launch for the 90 percent of the population

participating in SHI. The remaining 10 percent are covered by private health plans because of their employment status (i.e., self-employed) or income (gross income above €50,000 per year, or US\$70,663).³⁸ These individuals are reimbursed for drugs by these private plans. Decisions as to whether a service should be included in the catalogue of reimbursed services are made by the Federal Joint Committee (FJC). The FJC is a self-governing board comprising representatives of the national associations of SHI physicians who practice privately in an ambulatory setting, hospitals, SHI funds, and nonvoting patient representatives.³⁹ It is the responsibility of the FJC to establish reference pricing groups for drugs and drug classes.⁴⁰

Reference Pricing in Germany

The reference-pricing model was first introduced into the SHI system in 1989. The reference price is the maximum reimbursable price that the SHI is willing to pay; if a drug or a device subject to reference pricing is more expensive than the reference price, either the manufacturer must lower the price or the patients will have to pay the difference out-of-pocket. In 2004, the FJC decided to include the patented lipid-lowering drug atorvastatin in a reference-pricing group with cheaper, off-patent products of the same drug class, such as simvastatin.⁴¹ This was the first of what is known as a “jumbo reference-price group.” Since then, three further jumbo groups have been established: angiotensin II receptor antagonists, selective 5-HT_{1B/1D/1F}-receptor antagonists, and proton pump inhibitors.

FJC defines groups of drugs for reference-pricing purposes. A minimum of three drugs must be available on the market to initiate one of three different levels of reference-pricing groups: 1) same chemical agent, 2) pharmacologically comparable chemical agents with similar therapeutic effect, and 3) different chemical agents with the same therapeutic effect including combinations of drugs. As a next step, the national association of SHI funds sets the reference price for each of the groups following legal guidance as laid out in Germany’s Social Code Book V. Prices are published four times a year by the Deutsches Institut für Medizinisches Information und Dokumentation.⁴² Pfizer’s Norvasc

5mg, 30-pill pack, currently costs €27.17. A patient asking for the brand would have to pay the difference of €15.81 over the reference price. Yet, there are also products below the fix reference price, for instance Lansoprazol ABZ 30mg, 98-pill pack, is at €33.83 more than €20 below the reference price applicable to the size and dosage of this drug.

The Institute for Quality and Efficiency in Health Care

In 2004, the Institute for Quality and Efficiency in Health Care (IQWiG), modeled after the U.K.'s NICE, was established^{43,44} by the then Socialist and Green party coalition government. Over time, IQWiG has become a highly valued and respected source for the impartial compilation of scientific evidence for the FJC to address questions needed to steer the SHI system. Transparency is guaranteed as both experts and stakeholders are consulted at various stages. IQWiG makes recommendations that are not binding on the FJC. During the first few years, reports were limited to benefit assessment in accordance with the principles of evidence-based medicine—in effect providing comparative effectiveness research information. Currently, IQWiG is working on its first two commissions for full health economic analyses, using an approach methodologically different to those adopted in the U.K. and Australia. The evaluations focus on antidepressants⁴⁵ and the use of clopidogrel in acute coronary syndromes and peripheral arterial disease.⁴⁶

The New German Pharmaceutical Pricing Law

As of January 1, 2011, under AMNOG (an act to reorganize the drug market), all new drugs—with two exceptions specified below—must be assessed to determine their additional benefits over drugs for the same indication or therapeutic area prior to being launched in the German market. Drugs already in the market may be assessed if FJC requests an evaluation. The benefit assessment, which is based on a dossier submitted by the manufacturer at market entry, will inform the classification of the new drugs into six different groups: 1) major added benefit, 2) considerable added benefit, 3) minor

added benefit, 4) unquantifiable added benefit, 5) no added benefit, and 6) less benefit.

Under the classification system, if a drug shows additional clinical benefit, there will be negotiations on the price between the association of SHI funds and the manufacturer. Where the drug does not show additional benefit, it will be put into a reference-pricing group or will only be reimbursed at the price of a cheaper comparator drug. Orphan drugs for rare diseases and conditions, which may include oncology and end-of-life drugs, are exempt from the early benefit assessment if annual sales of the drug in the preceding 12 months do not exceed €50 million (US\$71 million).

If IQWiG's assessment shows additional benefit, and FJC agrees in its appraisal, the National Association of SHI funds⁴⁷ and the manufacturer will go into negotiations over a price. Any negotiated price will be binding for all German SHI funds. For the first time in Germany, the outcome will also extend to private health funds. Individual funds may also negotiate further discounts or rebates with manufacturers. Should the two negotiating parties not come to an agreement within six months of FJC's decision on additional benefit, a central board of arbitration will determine a rebate based on international prices. Nonetheless, the official list price that the manufacturers set at the time of market entry remains the reimbursement price until one of the price negotiation processes described above has been concluded. Moreover, the official list price will not be modified. As a result, other European countries cannot rely on a lower German list price in their negotiations or when applying external reference pricing.⁴⁸

Benefit Assessment of Drugs: Choosing Outcome Measures

IQWiG relies strictly on patient outcomes—such as effects on mortality, morbidity, and quality of life—in its benefit assessments, and avoids unvalidated or inadequately validated surrogate measures.⁴⁹ However, with the AMNOG law, surrogate measures may be used in dossiers as the duration of studies to support early market access do not always allow for patient outcomes to be measured. As a result, in August 2010, the FJC

commissioned IQWiG to undertake a rapid review of the validity of surrogate endpoints in cancer treatment. IQWiG’s report presented an assessment of best practice in surrogate endpoint validation.⁵⁰ The report considered breast and colon cancer studies and concluded that the validity of surrogate measures such as disease-free survival remains unclear for both types of cancer mainly as there was not sufficient correlation between effects on disease-free or progression-free survival and overall survival.⁵¹ It is currently being considered by the FJC to inform its understanding of how surrogate endpoints may be used in the benefit assessment of oncology drugs.

In regard to dementia,⁵² IQWiG has applied the concept of a minimally important difference to distinguish between treatment differences on scales that are statistically significant but clinically unimportant or irrelevant. Applying this concept to binary outcomes, for example, in oncology, this could mean that a drug that creates a statistically significant but small gain in average overall may be considered to have little clinical relevance. However, at present, with regard to cancer drugs, IQWiG considers any statistically significant gain in average overall survival as added benefit. Nevertheless, IQWiG could downgrade the level of added benefit of an oncologic drug given, for instance, a considerable decrease in quality of life that results from the therapy.

Rationing, Prioritization, and Efficiency Gaps

A vigorous ethical debate has been taking place over the last two years in Germany about what the health care system ought to make available and for whom. Stakeholders’ motives vary. Some physicians want to reduce the basket of SHI-covered services to increase their incomes through services that they can offer and for which they can charge a premium. Some ethicists and lawyers want to raise awareness that scarce resources need to be distributed according to ethically sound principles that are also consistent with constitutional principles. A number of nationwide research projects have been instigated and various meetings and conferences convened, raising questions about oncology and end-of-life drugs. What should be considered a relevant effect of a drug? Who should

judge whether the effect is relevant, the patients or the public? Should the relevance of an effect be determined by absolute or relative prolongation of survival? Does the FJC have a legal right to make these decisions under constitutional law? Other stakeholders view the entire direction of the debate as a misstep, citing more pressing and less contentious opportunities for gaining greater efficiency. These include: excluding from the reimbursement package treatments for which there is no proof of benefit according to criteria of evidence-based medicine, reducing the number of hospital beds, and revising regulations around inpatient and outpatient care that currently give rise to duplication and waste.

While the United Kingdom and Australia have well-established mechanisms for using comparative clinical and cost-effectiveness to inform technology adoption, Germany has only recently started to move in this direction, through both institutional and legal reforms. Germany is still searching for solutions that are transparent, efficient, and respectful of prevailing ethical values and legal standards, and of the country’s historical legacy.

EMERGING THEMES: SHARED CHALLENGES AND INTERNATIONAL APPROACHES

In 2009, discussing the clinical effectiveness and cost of new cancer treatments, Fojo and Grady⁵³ estimated that if “a survival advantage of 1.2 months is worth \$80,000, and by extrapolation survival of one year to be valued at \$800,000, we would need \$440 billion annually—100 times the budget of the National Cancer Institute—to extend by one year the life of the 550,000 Americans who die of cancer annually. And no one would be cured.” Specialty drug costs are growing in the United States, as they are in Europe and Australia (Exhibit 4). However, in the U.S., rising costs often lead to cost-shifting to patients and their families either through premium increases, higher copayments, or both.^{54,55,56} Recent attempts by the Obama administration to introduce comparative effectiveness research as a means of informing clinical and policy decisions, albeit in a very passive and voluntary fashion, have been met

Exhibit 4. Per Capita Spending on Pharmaceuticals in the United Kingdom, Germany, Australia, and the United States, 2000 and 2008

	U.K.		Germany		Australia		U.S.	
	2000	2008	2000	2008	2000	2008	2000	2008
Per capita spending on pharmaceuticals [US\$ PPP]	259.8	381.4	362.2	594.2	335.5	502.8	540.3	919.1
Growth [%]	46.81		64.1		49.87		70.11	
Percentage of total government health expenditure	14.2	11.6	13.6	15.0	14.8	14.6	11.3	11.9

Note: US\$ PPP = U.S. dollar purchasing power parity, an estimate of the exchange rate required to equalize the purchasing power of different currencies, given the prices of goods and services in the countries concerned.

Source: 2011 OECD Health Data, http://www.oecd.org/document/16/0,3746,en_2649_34631_2085200_1_1_1_1,00.html.

with resistance. Moreover, any hint of the Medicare Independent Payment Advisory Board considering prices in the context of containing overall health expenditure or of Medicare using its negotiating power when purchasing pharmaceuticals have had an equally hostile reception.⁵⁷

Balancing access to needed medicines against escalating costs is one of the most challenging tasks in health care reform. The continually evolving pharmaceutical pricing and reimbursement policies of the United Kingdom, Germany, and Australia, are intended to help bridge that balance. In the U.K. and Australia, value-for-money remains at the heart of policymaking, especially in the current financial climate, and it is becoming increasingly important in Germany, one of Europe's more generous health care systems (Exhibit 5). In the U.K., nearly 12 years after it was established, NICE is seen by government—as well as the drug industry, patients, and professionals—as crucial to maintaining the quality and sustainability of the system. EOL guidance, the Cancer Drugs Fund, and the value-based pricing proposals all consider costs and evidence and are being broadly and publicly consulted and debated before they are implemented. In Australia, the PBAC enjoys political and popular support, and similar methods of health technology assessment are applied to other health care interventions such as vaccines, medical devices, and diagnostics.

Despite the differences among countries—with Germany providing a more generous package and applying a different disease-specific scope for economic

analyses—a number of common emerging themes can be identified:

- Irrespective of the funding mechanism (social insurance or tax-based), all three countries view access to medicines as an entitlement for their populations; in doing so they find it legitimate to limit cost-shifting to patients to some degree, as they include new medicines on their pharmaceutical formularies.
- All three countries have developed explicit mechanisms for making listing and reimbursement decisions based on evidence of comparative clinical and cost-effectiveness, notwithstanding that economic evaluation has only recently been introduced in the German system.
- All three systems struggle with the cost of some specialized drugs, especially oncology drugs for patients with advanced disease. In response, they have developed exceptional mechanisms, which include special pricing, risk-sharing arrangements, and tailored coverage determinations to facilitate access while considering value-for-money and negotiating prices based on evidence of comparative effectiveness.
- Value-for-money in the health system is an acceptable principle underpinning decision-making in all three countries.

Exhibit 5. Overview of the Three Systems

Attribute	Australia	Germany	United Kingdom
Percentage of GDP spent on health (2008)*	~ 8.7%	~ 10.7%	~ 8.8%
Percentage of deficit in health budget	N/A	Differs from year to year, with both surpluses and deficits in various years.	0%. The NHS is required statutorily to break even.
Funding source	General taxation and Medicare levy	Contributions from employers and employees in the SHI scheme	General taxation
Percentage of total health expenditures on pharmaceuticals (2008)*	~ 14.6%	~ 15.1%	~ 11.6%
National (or regional) mechanism for assessing the comparative clinical and cost-effectiveness of new medicines	Pharmaceutical Benefits Advisory Committee responsible for assessing comparative cost-effectiveness and recommending medicines that should be subsidized.	Federal Joint Committee or Institute for Quality and Efficiency in Health Care responsible for assessing the comparative effectiveness of new pharmaceuticals within an early benefit assessment.	National Institute for Health and Clinical Excellence (NICE) responsible for assessing comparative clinical and cost-effectiveness for all major new molecular entities or major new indications launched in the NHS.
Mechanism for pricing and reimbursement	Reimbursement subject to determination of cost-effectiveness. Prices also subject to negotiation and risk-sharing agreements. Free pricing of private prescriptions.	Currently, free, company-set pricing in the first year after market launch, while manufacturer and National Association of Statutory Health Insurance Funds negotiate final price based on early benefit assessment.	Currently, free company-set pricing. Some indirect price negotiation through NICE Patient Access Schemes. Local price-volume agreements with providers.
Copayment levels	Two levels of fixed copayments; up to AUD34.20** per item for general beneficiaries, AUD5.60 per item for concessional beneficiaries (2011) with caps to protect against catastrophic expense.	10% copayment to max of €10 (US\$14). Patients eligible for exemption if the copayment reaches 2% of the annual gross income (1% for chronically ill).	~£7 (US\$11) per prescription. ~85% of patients eligible for exemption because of age, chronic disease, employment status, etc.
Mechanism for coverage/listing decisions	Positive list. Addition to the formulary only possible with PBAC recommendation.	All licensed drugs except “lifestyle” drugs are in principle covered by the statutory health insurance funds.	All licensed drugs are in principle covered by the NHS.
Explicit exceptions to listing/coverage mechanism	Herceptin Program Life Saving Drugs Program	N/A	Exceptional panels operate at the local trust level. End-of-life NICE guidance for more generous threshold for drugs extending life for terminally ill patients. Cancer Drugs Fund for cancer drugs considered and rejected by NICE.

* 2011 OECD Health Data, http://www.oecd.org/document/16/0,3746,en_2649_34631_2085200_1_1_1_1,00.html.

** AUD1 = USD1.03368 as at April 1, 2011. From <http://www.oanda.com>.

Source: Authors' analysis.

- There is increasing support for accelerating processes for new drugs coming to the market, with payers working with pharmaceutical companies to ensure products are appropriately priced and the risks of early adoption shared, through patient access scheme arrangements that may require manufacturers to generate and analyze new evidence on comparative clinical and cost-effectiveness as these drugs are used in a real-world setting.

The United States is also starting to struggle with questions of access and sustainability. For end-of-life or expensive oncology drugs, the experiences of the United Kingdom and Australia raise questions that the U.S. and other health care systems may wish to consider as they push reform plans forward:

- Is it legitimate to single out certain conditions, which weigh more in terms of the value society places on them and therefore attract more resources relative to less “important” conditions?
- Who decides what is “important” and what would have to be displaced in terms of services and technologies in order to accommodate these high-priority conditions?
- How should the evaluation and funding of such technologies differ from other categories of drugs and treatments? Should the standards of evidence be lower? And what impact would such a policy have on the drive to generate good-quality evidence in the medium and long term?
- What are the implications for research and development and for encouraging the development of high-impact technologies when technologies that have limited health impact are rewarded more highly than others that deliver a greater degree of health improvement?
- What are the roles of patient and disease-specific advocacy groups and public and media buy-in in developing and implementing these policies?

The United States, Western Europe, and Australia may have different underlying principles when it comes to health care, but they are faced with similar problems of rising costs, inequities of access resulting in inefficiencies, burgeoning spending, and varied efforts by policymakers to manage these tensions. In the U.S., there are no explicit nationwide coverage decisions that are enforceable across public and private providers. And while public-payer spending grew six times faster in 2009 than did private health insurance (and is due to exceed the latter by 2012⁵⁸), it is unlikely that a nationwide coverage decision mechanism will be established in the foreseeable future. Nevertheless, there are at least three themes from Europe and Australia that U.S. policymakers may find useful:

- The relevance of evidence in making decisions. Whatever the payment system and however fragmented it may be compared with other countries, there must be a legal, political, and institutional framework that encourages the use of evidence in making decisions on what to include in public or private benefit packages. The establishment of the Patient-Centered Outcomes Research Institute is a step in the right direction. Its work, coupled with appropriate incentives (monetary, regulatory, reputational, and other) may speed the diffusion and uptake of published data, and have an impact on outcomes and costs.
- The importance of price negotiations and risk-sharing arrangements in ensuring broader access, value-for-money, cost control, and financial sustainability (e.g., through affordable insurance premiums and healthy tax rates). Medicare’s Independent Payment Advisory Board may serve as a valuable lever, especially if it is allowed to discuss prices with the product developers, based on evidence of effectiveness pertinent to Medicare’s population. Such a process, if conducted transparently, may also serve as an incentive for industry to generate evidence of value through commercially sponsored comparative effectiveness research. Indeed, the experience of

the U.K.’s NHS with risk-sharing—though not without problems—shows that early engagement with industry can trigger not only price reductions but also a discussion of the evidentiary requirements and of ways of addressing these as products are adopted. For such discussions between payers and developers to have a greater impact, they may need to take place earlier in the developmental cycle of products, before licensing, and with input from the regulators. Such discussions are already occurring on a very limited basis in Australia, with a series of meetings between the manufacturer, the regulator, and the funder before commencement of Phase III trials. The focus of these discussions is not on pricing issues but on determining the best ways to address the evidentiary needs of both the regulator and the funder efficiently. Similarly, in the United Kingdom, NICE has been running a scientific advice program over the past three years, with similar objectives.

- The role of open public debate and engagement with all stakeholders to discuss values, evidence, methods and processes for making unavoidable prioritization decisions. Politicians and government, as well as industry representatives and professionals, must be honest about the issues and engage in dialogue rather than dismissing attempts

to rationalize spending as “rationing,” “death panels,” or “socialized medicine.” Misinformation about single-payer systems and the use of health technology assessment in decision-making is distracting and polarizing. In most industrialized countries, as well as in a growing number of emerging markets, industry, payers, professionals, and patients have come together to discuss the difficult issue of health care priority-setting.

Politics is about compromise, and prioritization decisions cannot and should not be determined solely by scientific calculations. Judgments must be made. The choice facing all countries, including the United States, is between making such judgments in a transparent, rational and inclusive way, offering the chance to be heard to all those affected by them, or making them covertly, where neither the scientific nor the social values applied can be understood or challenged. There is a third, even less constructive option of pretending that such judgments do not need to be made at all. The U.S. must find a way to move past its profound reluctance to “systematically deny access to expensive treatments that extend life by only a few weeks . . . [and recognize that] the morality of refusing to make deliberated choices is itself questionable.”⁵⁹

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